

## Impact of rem-related obstructive sleep apnea therapy on anxiety, depression and daytime sleepiness

Impact of rem-related OSA therapy

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### Abstract

**Aim:** Obstructive Sleep Apnea (OSA) is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep. Patients who slept at least 30 minutes in REM sleep, total apnea-hypopnea index (AHI)>5 and REM AHI/NREM AHI>2 are defined as REM-related OSA. We investigated the efficacy of treatment on anxiety, depression and daytime sleepiness in REM-related OSA.

**Material and Methods:** A total of 110 patients with REM-related OSA participated in the study. Patients were divided into two groups; the treatment group consisted of patients who received treatment (n:38) and the non-treatment group who refused to receive treatments (n:72). Of the 38 patients treated, 33 had mild disease and 5 had moderate disease. Sixty-seven of the 72 patients who did not receive treatment had mild disease and 5 had moderate disease. Both groups completed the HADS (Hospital Anxiety-Depression Scale), ESS (Epworth Sleepiness Scale) questionnaires. SPSS was used for data analysis. Results were expressed as mean and standard deviation. T-test and chi-square tests were performed to compare cases. A p-value <0.05 was considered statistically significant.

**Results:** There was no statistically significant difference between the groups, in terms of age, gender, height, weight, and body mass index (BMI). No statistically significant difference was found between the two groups in terms of polysomnography parameters AHI, REM AHI, arousal index, periodic leg movement (PLM) index, sleep latency, REM latency, minimum oxygen saturation (SPO<sub>2</sub>), and cumulative percentage of time spent at saturation below 90%. HADS- Anxiety, HADS- Depression and ESS scores were significantly higher in the non-treatment group in comparison to the treatment group (p=0.011, p=0.016, p=0.005, respectively).

**Discussion:** The results of our study showed that treatment has positive effects on anxiety, depression and daytime sleepiness, which are indicative of the quality of life in patients with REM-related OSA.

### Keywords

REM-Related OSA, Anxiety, Depression, Treatment, APAP

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## Introduction

Obstructive sleep apnea (OSA) is a syndrome characterized by recurrent episodes of partial (hypopnea) or complete (apnea) upper respiratory tract obstruction during sleep [1]. The REM (rapid eye movement) sleep covers 20-25% of all sleep time. During this stage of sleep, cardiorespiratory disorder, respiratory control disorder, and irregular ventilation occur [2]. Therefore, in patients with OSA, the number and duration of obstructive respiratory events increase as a result of severe oxygen desaturation during REM sleep.

Patients who slept at least 30 minutes of REM sleep, total apnea hypopnea index (AHI) > 5, REM AHI / NREM AHI  $\geq$  2, NREM AHI < 5 are defined as REM-related OSA [3]. REM-related OSA was described in 1996 by Kass et al. and constitutes 10-36% of all OSA cases. REM-related OSA is more common in mild to moderate OSA [4].

REM-related OSA has been associated with more severe cardiovascular side effects than classic OSA. In the Wisconsin Sleeping Cohort, it was reported that REM-related OSA was associated with hypertension [5]. Another study found that OSA patients with a longer duration of obstructive apnea had more severe hypertension compared to patients with a shorter apnea duration [6]. Furthermore, REM-related OSA was associated with type 2 diabetes [7]. Sleeping disorders are important risk factors for the development of depression. Gupta et al. showed an increased prevalence of OSA in people with and post-traumatic stress disorder and major depressive disorder [8]. REM-related OSA was associated with anxiety and depression [9]. The clinical significance of REM-related OSA has been underestimated and under-investigated for a long time and therefore it remained untreated. As a result, there are limited data on the efficacy of REM-related OSA therapy. Therefore, in our study, we planned to investigate the efficacy of treatment on anxiety, depression and daytime sleepiness in patients with REM-related OSA.

## Material and Methods

Patients who applied to the Sleep Disorders Center of the Inonu University and Malatya Training and Research Hospital between 2017 and 2018 were evaluated retrospectively. All patients who underwent polysomnography were informed about the planned study before the procedure. It was explained that the data will be used in the study. The patients were asked whether they accepted voluntary participation or not, and a consent form was obtained from them if they agreed. The study was in accordance with the Helsinki Declaration, and it was approved by the Ethics Committee of the Medicine Faculty of Inonu University (issue:2018/22-4).

Additionally, patients with REM sleep time less than 30 minutes, total sleep activity less than 70%, and diagnosed with COPD or asthma were excluded from the study. Patients with a history of depression and antidepressants use were not included in the study.

A total of 110 patients with REM-related OSA were enrolled in the study. Patients were divided into two groups; the treatment group consisted of patients who received treatment (n:38) and the non-treatment group consisted of patients who refused to receive treatments (n:72). The group receiving treatment

consisted of patients who had been receiving treatment for at least six months as of the date of the survey. Both groups completed the HADS (Hospital Anxiety-Depression Scale), and ESS (Epworth Sleepiness Scale) questionnaires.

Polysomnography (PSG): Patients were evaluated using a 55-channel polysomnography (Alice 6<sup>®</sup> Sleepware, Philips Respironics, PA, USA) system. Sleep recordings were analyzed according to the guidelines published by the American Academy of Sleep Medicine (AASM) [10].

AHI was obtained by dividing the sum of the apnea and hypopnea numbers by the sleep duration in hours. Sleep stages were scored as N1, N2, N3, and REM sleep. The REM latency is the time before the first REM phase. The desaturation index was defined as a 3% reduction in oxygen saturation (SPO<sub>2</sub>) from baseline, with the minimum SPO<sub>2</sub> being the lowest SPO<sub>2</sub> recorded overnight.

Hospital Anxiety-Depression Scale: HADS consists of two subscales, one of which consists of seven items measuring anxiety and the other seven items measuring depression, which are scored separately. The questionnaire consists of 14 parameters. The Likert scale was used (usually 3 points, often 2 points, sometimes 1 point, never 0 points). Total scores  $\geq$ 10 are considered positive for anxiety, and scores  $\geq$ 7 are considered positive for depression.

Epworth Sleepiness Scale: We used the Epworth Sleepiness Scale as it is a questionnaire used to evaluate daytime sleepiness in patients with sleep disorders. It is an 8-item questionnaire with scores between 0 and 24. A score of 10 or higher on the Epworth Sleepiness Scale is an indicator of excessive daytime sleepiness.

Statistical analysis: SPSS was used for data analysis. Results were expressed as mean and standard deviation. T-test and chi-square tests were performed to compare cases. A p-value <0.05 was considered statistically significant.

## Results

A total of 110 patients with REM-related OSA were included in the study. Of the 38 patients who received treatment, 33 had mild disease and 5 had moderate disease. Sixty-seven of the 72 patients who did not receive treatment had mild disease and 5 had moderate disease.

Twenty-one patients received APAP (Automatic Positive Airway Pressure Therapy), 15 patients received surgery (nasal surgery, tonsillectomy), 1 patient used an oral appliance treatment, and 1 patient received APAP treatment after nasal surgery. The treatment group consisted of patients who used APAP for a minimum of 4 hours per day and used APAP in more than 70% of the sleep time over 6 months after the initiation of the treatment. The daily duration of the usage of APAP device was checked by analyzing the recorded data. Gender, age, weight, height and body mass index (BMI) of all patients were recorded. There was no statistically significant difference between the two groups in terms of gender, age, height, weight and BMI. No statistically significant difference was found between the two groups in terms of polysomnography parameters AHI, REM AHI, PLM (periodic leg movement) index, arousal index, REM latency, sleep latency, minimum SPO<sub>2</sub>, and desaturation index (Table 1). Anxiety score was significantly higher in the non-treatment

**Table 1.** Baseline features and polysomnographic variables in patients with REM-related and NREM-related OSA

	Treatment	Nontreatment	p (t-test)
	group (n:38)	group (n:72)	
Age years (mean ± SD)	46,4±11,0	47,3±9,6	0,196
Gender (male/female)	21/17	29/43	0,133
BMI kg/m2(mean ± SD)	31,7±6,9	30,7±4,5	0,48
AHI (events/h)	11,3±4,2	9,2±4,5	0,08
REM AHI (events/h)	45,7±22	32,5±15	0,492
Arousal Index (events/h)	6,9±3,2	7,1±3,2	0,666
PLM Index (events/h)	21,6±35,2	14,1±32,1	0,389
Sleep Latency (min)	28,1±38	28,2±22	0,1
REM Latency (min)	127,5±66	135,7±78	0,241
Minimum SPO2 (%)	82,3±5,9	82,9±6,3	0,134
Desaturation Index (%)	7,4±5,5	6,0±8,1	0,069
Total	38	72	110

**Table 2.** Results of Anxiety, Depression and Epworth Scale

HADS and ESS	Treatment	Nontreatment	p (Chi-square)
	group (n=38)	group (n=72)	
Anxiety Scale			
<10	30	39	0,011
≥ 10	8	33	
Depression Scale			
<7	25	30	0,016
≥ 7	13	42	
Epworth Scale			
<10	25	27	0,005
≥10	13		

(Anxiety ≥10 positive, depression ≥7 positive, ESS ≥10 daytime sleepiness)

group in comparison to the treatment group ( $p=0.011$ ). Depression score was statistically significantly higher in the non-treatment group in comparison to the treatment group ( $p=0.016$ ). The ESS score was significantly higher in the non-treatment group in comparison to the treatment group ( $p=0.005$ ) (Table 2).

## Discussion

In our study on REM-related OSA patients, anxiety, depression and ESS scores were significantly higher in the non-treated group. Currently, CPAP (Continuous Positive Airway Pressure Therapy) treatment is the gold standard method for the management of OSA [11]. Although CPAP treatment is recommended for patients with moderate to severe OSA (AHI>15/h), it is also recommended in patients when the symptoms are prominent and/or cardiovascular or cerebrovascular risk factors and severe oxygen desaturation during the night are present, even if OSA is mild (AHI: 5-15/h). However, general precautions (weight loss, non-supine position, alcohol and sedatives to avoid, treatment of concomitant diseases, etc.), oral appliance treatment, and nasopharyngeal surgery are also alternative treatment methods in suitable patients [12]. Actually, CPAP treatment is symptomatic therapy. Therefore, it is important to maintain adherence to CPAP, to estimate CPAP compliance before starting the treatment, and to use intensive interventions in patients who are not eligible for CPAP use. Various studies have

shown that the severity of the disease, the degree of daytime sleepiness before treatment, gender, age, and PAP pressure are clinical determinants of adherence to CPAP use [11,12]. Although CPAP treatment has high efficacy, currently, the major problem with CPAP treatment is that a significant proportion of patients does not accept CPAP or have low compliance with treatment. Compliance rates vary between 29% and 81%. Although there are differences in the definition of compliance with CPAP therapy, patients who use CPAP more than 70% of the night and 4 hours per night are generally regarded as compliant [13]. It has been shown that oral appliance treatment reduces AHI and improves oxygenation at night [14]. In patients who cannot tolerate CPAP may also be considered as a treatment option. In a study conducted with an oral appliance, the treatment showed similar efficacy in REM-related and NREM-related OSA patients in terms of therapeutic efficacy [15]. Oral appliance treatment therapy, which can reduce daytime sleepiness, may be recommended for the treatment of patients with mild-to-moderate OSA. One of the treatment modalities in OSA is surgical treatment. Surgical interventions may be an option in patients who cannot tolerate CPAP and may be used as an alternative method in selected patients. In a multi-center study by MacKay et al, patients with moderate to severe OSA who failed CPAP have undergone palate and tongue surgery. Six months after the surgical operations performed on these patients, it was shown that patients experienced significant improvement in AHI and daytime sleepiness [16]. The most appropriate patients for either oral appliance therapy or surgical treatment are those with simple snoring or mild OSA. Surgical interventions can also be used in patients who cannot tolerate or accept CPAP treatment, even if they have moderate or severe OSA. Surgical treatment and oral appliance treatment can be considered as an alternative treatment for OSA patients in patients who do not want to use a CPAP device due to aerosolization during the COVID-19 pandemic period. REM phase of sleep accounts for about a quarter of the total sleep time in healthy adults, and is mostly intensified in the second half of the sleep period. NREM sleep accounts for about 80% of total sleep. Regardless of being REM-related or not, patients with OSA experience more severe respiratory events during REM sleep [17]. Therefore, REM-related OSA is treated with APAP because patients with REM-related OSA require relatively lower pressure over a long period of total sleep and higher pressures during the REM sleep period. In addition, fluctuations in pressure due to disproportionate distribution of respiratory events during sleep are one of the most important factors that may affect CPAP compliance. Since the recommended 4-hour treatment for CPAP therapy may not be sufficient in REM-related patients due to the fact that REM sleep is seen especially towards morning, it may also be necessary to use the device for a longer period of time. REM-related patients are reluctant to use CPAP because they are mainly mild-moderate. In these patients, suggesting oral appliance treatment or surgical treatment seems to be appropriate to improve treatment compliance. In a study evaluating CPAP treatment, the presence of REM-related OSA was shown to be an independent risk factor affecting CPAP compliance. They claimed that CPAP treatment compliance

was better in normal OSA than REM-related OSA and the REM AHI / NREMAHI ratio was the most important factor affecting compliance [18]. In a recent study, twenty REM-related OSA patients who were given APAP treatment were followed up for a year in terms of quality of life. Patients were evaluated with ESS, FOSQ, psychomotor vigilance test reaction time (PVT-RT), and Depression Anxiety Stress Scales (DASS-21) questionnaires at 1, 3, 6, and 12 months after treatment, and APAP treatment reduced daytime sleepiness and increased quality of life [19]. The results of these studies are similar to the results of our study.

Sleep studies have shown that depression is associated with altered sleep architecture and REM sleep disturbance. Increased REM duration, increased REM intensity, and shortened REM latency, have been considered biological markers of depression [20]. Insomnia, which is correlated with depression, is seen in 39-58% of OSA patients. It has also been reported that 80% of patients with depression suffer from insomnia [21]. In a study investigating the effect of insomnia, REM-related OSA and normal OSA patients were compared with the ESS and Pittsburgh Sleep Quality Index (PSQI), and as a result, high PSQI was found in REM-related female patients, and no difference was found between the groups in terms of ESS [22]. Koc et al in their study with patients with similar AHI, showed that morning headache was more common in the group with high AHI in the REM period compared to those with a lower, and daytime sleepiness was higher in the group with a morning headache [23]. In a meta-analysis, Sanchez et al., concluded that treatment with CPAP or oral appliance treatment in OSA was superior to placebo for the treatment of depressive symptoms [24]. In a review by Povitz et al., it was shown that use of both CPAP and oral appliance treatment for OSA treatment resulted in improvements in depressive patients [25].

The patients in our study were statistically similar in terms of age, gender, BMI and polysomnography data in both groups. However, there were some limiting factors. The cases were screened retrospectively. There was no standardization of the environment the patients lived in and the emotional situation they experienced during the study period, and there was no objective evaluation of other conditions that could cause depressive mood was done.

### Conclusion

The results of our study showed that treatment has positive effects on anxiety, depression and daytime sleepiness, which are indicative of the quality of life in patients with REM-related OSA. Encouraging patients to receive treatment and assuring continuity will decrease sleep deprivation while improving the quality of life. Although, it is still not possible to eliminate OSA using a single method or a combination of multiple methods, it may be possible to define the patient's needs and increase the compliance with the treatment of OSA by patient-targeted approaches with participation of patients in all processes. Further studies with larger series are needed to support these results.

### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and

approval of the final version of the article.

### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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### Conflict of interest

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